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Sir:

Transmitted herewith for filing is the patent application of

Inventor: James J. Gibbons, Jr.

For: Method of Potentiating Chemotherapy and Treating Solid Tumors

This application is a:

New Application CIP Application

Divisional Application **Continuation Application**
of prior application No. _____. The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference.

Enclosed are:

_____ sheets of drawing.

Information Disclosure Statement.

Preliminary Amendment.

Signed statement attached deleting inventor(s) named in the prior application

| CLAIMS AS FILED | | | | |
|------------------------------|---------------------|---------------------|-------------|----------------------------------|
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- The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application to American Home Products Corporation Deposit Account No. 01-1425.

Arnold S. Milowsky
Reg. No. 35,288
September 12, 2000

**METHOD OF POTENTIATING CHEMOTHERAPY AND
TREATING SOLID TUMORS**

5

This application claims the benefit of U.S. Provisional Application No. Not Yet Known, which was converted from U.S. Patent Application No. 09/396,051, filed September 15, 1999, pursuant to a petition filed under 37 C.F.R. 1.53(c)(2)(i).

10

This invention relates to the use of a combination of a bioresponse modifier and a chemotherapeutic agent in the potentiation of chemotherapy and in the treatment of solid tumors.

15

Cancer chemotherapy for solid tumors has historically been focused on cytotoxic drugs that target essential metabolic processes (anti-metabolites) or general toxins (alkylating agents) that interfere with multiple metabolic processes. Antibiotic based drugs (doxorubicin, mitoxantrone, mitomycin C, etc.) target nucleic acid replication or integrity and are, therefore, generally toxic to cells. Similarly, microtubule active (taxanes, vinca alkaloids) compounds target structurally essential components of the cell, rendering these compounds generally toxic as well.

20

The trend in recent years toward combinations of drugs with somewhat different mechanisms of action has improved the response rate and survival for some solid tumors, including breast, prostate, and small cell lung cancer. Nevertheless, most solid tumors display a poor response rate with little demonstrable effect on survival. Included in this group of cancers are non-small cell lung, head and neck, stomach, pancreatic, cervical, melanoma, adrenal cortex, and soft tissue sarcomas. For these solid tumors in particular, and for solid tumors in general, new therapies are needed.

30

U.S. Patent 5,312,831 discloses urethanes and ureas which induce cytokine production, that are useful in restoring neutrophils after cancer chemotherapy,

radiation therapy, bone marrow transplantation, or infections, and are useful in the treatment of cancer, AIDS, aplastic anemia, myelodysplastic syndrome, infectious diseases, and the enhancement of the immune response.

U.S. Patent 4,666,890 discloses a synthetic tripeptide which has been reported

5 to have activity as an immunomodulator, for use as an antitumor agent rather than as an adjuvant to chemotherapy. The reported cell-wall components and their synthetic analogs are all peptides incorporating a D-glutamic acid (D-Glu) moiety q-linked to either lysine (Lys) or diaminopimelic acid (A2pm), with additional peptide bonds or fatty acyl groups flanking the two ends.

10

DESCRIPTION OF THE INVENTION

This invention provides a method of treating solid tumors which comprises administering an effective amount of a combination of (1) a bioresponse modifier and (2) a chemotherapeutic agent. This invention also provides a method of potentiating

15 the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a chemotherapeutic regimen. As used in this invention, the term a bioresponse modifier and a chemotherapeutic agent includes the administration of one or more agents of each category; thus, for example, the term a chemotherapeutic agent can include the

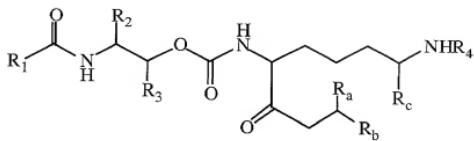
20 administration of two chemotherapeutic agents.

Treating is defined as providing palliative treatment, or inhibiting the growth or eradicating the solid tumor for which treatment is administered.

25 For the purpose of defining the scope of this invention, a bioresponse modifier is an agent which activates the body's innate immune system, and typically includes cytokine inducers and immune adjuvants. Cytokine inducers are agents which induce the production of cytokines, and include cytokines such as IL-1, TNF; natural products such as muramyl dipeptide, lipopolysaccharide and beta-glucan; and synthetic

30 cytokine inducers such as those disclosed in U.S. Patents 5,312,831, and 4,666,890, the disclosures of which are hereby incorporated by reference. Cytokine inducers are the preferred bioresponse modifiers of this invention.

Particularly preferred cytokine inducers are those disclosed in U.S. Patent 5,312,831 of Formula I, having the structure:



5

wherein

R₁ is selected from the group consisting of hydrogen, a substituted or unsubstituted (C₁-C₂₀) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene

10 group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

15 R₂ and R₃ are independently selected from hydrogen, substituted or unsubstituted (C₁-C₆) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R₃, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;

20 25 R₂, R₃ and R₄ are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxyamide;

X is oxygen or nitrogen;

R₄ is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyarylalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxy carbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfonyl, aralkylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1- 4 hetero atoms selected from nitrogen, sulfur and oxygen;

or a pharmaceutically acceptable salt thereof.

The definitions of the substituents and methods of preparing the compounds of Formula I are provided in US Patent 5,312,831. The cytokine inducers of Formula I may contain one or more asymmetric carbons atoms; in such cases, the compounds of Formula I cover the individual diasteromers, the racemates, and the individual R and S enantiomers thereof.

It is particularly preferred that the cytokine inducer is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof (a compound of Formula I), which is disclosed as Example 28 of U.S. Patent 5,312,831.

U.S. Patent 5,312,831 discloses several standard pharmacologic test procedures which will enable one skilled in the art to evaluate whether compounds are bioresponse modifiers. For example, the test procedures in col. 16-17, evaluate the induction of IL-6, CSF, and G-CSF production.

It is preferred that the chemotherapeutic agent is a microtubular agent or a macrophage activating agent. Microtubular active compounds are defined as compounds that destabilize microtubules either by preventing polymerization of the protein tubulin (e.g., vincristine) or by preventing the depolymerization of tubulin

(e.g., taxanes). The assembly and disassembly of microtubules is a dynamic process influenced by tubulin binding proteins and protein phosphorylation (kinases). Microtubular active compounds include taxanes, such as paclitaxel or docetaxel, vincristine, vinblastine, vinorelbine, and the like. Macrophage activating agents are 5 those compounds which activate macrophage activity, such as adriamycin, doxorubicin, and similar anthracenediones and anthracyclines, cisplatin, carboplatin, mitomycin C, bleomycin, and the like. It is preferred that the chemotherapeutic agent is paclitaxel or carboplatin, or a combination of both. The microtubular agents or macrophage activating agents of this invention are either commercially available or 10 can be prepared by standard procedures in the published literature.

The potentiating effect of bioresponse modifiers on chemotherapeutic agents was evaluated in an in vivo standard pharmacological test procedure in which a human non small cell type lung cancer (NSCLC) cell line was engrafted onto the 15 flanks of immunodeficient nude mice. The following briefly describes the test procedure used and results obtained. $[R-(R^*,R^*)]-N-[(R)-6-Carboxy-N^2-[(2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine$ was used as a representative bioresponse modifier and paclitaxel was used a representative chemotherapeutic agent.

20 Balb-c nu/nu female mice were obtained from Charles River Laboratories at 6-8 weeks of age and used experimentally at 8-10 weeks of age. The human non small-cell lung carcinoma (NSCLC) line H-157 was obtained from the American tissue culture collection (ATCC) (Bethesda, MD). Cells were grown in RPMI medium with 10% fetal bovine serum.

25 Mice were injected subcutaneously with 7.5×10^6 H-157 NSCLC tumor cells. Tumors were allowed to develop until they reached a size of 80-150 mg. Tumor size was determined using vernier calipers to measure length (l) and width (w). The tumor volume was estimated using the formula $l \times w^2/2$. The volume in mm^3 can be 30 converted to milligrams directly assuming unit density. Seven days after injection, mice were randomized (day 0) into groups of 10 with a mean tumor mass of 100 mg. Treatment groups received paclitaxel (30 mg/kg) on day 0 and either vehicle or $[R-$

(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine (100 μ g/kg) on days 1 and 8.

On days 7 and 14, tumor growth in groups receiving paclitaxel plus [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine (100 μ g/kg) on days 1 and 8.

5 On days 7 and 14, tumor growth in groups receiving paclitaxel plus [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine was significantly inhibited versus untreated controls or groups receiving paclitaxel only. Paclitaxel alone inhibited tumor cell growth measured on day 7 (p≤0.05 by student's t test) and the degree of suppression was significantly enhanced by treatment with [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine one day after paclitaxel administration. By day 14, tumor growth in the paclitaxel only group was not significantly suppressed versus control; however, the group receiving paclitaxel on day 0 and [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine on days 1, 8 was still significantly suppressed when compared either to untreated controls or 10 the paclitaxel only group. The results obtained are shown below in Table 1. In the below table, [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine is referred to as CI.

15

20 TABLE 1. The Effect of CI on Paclitaxel Mediated Inhibition of
Tumor Cell Growth in Nude Mice Xenografts

| Treatment Group | Tumor size (mg) Day 7 | % Suppression | Tumor size (mg) Day 14 | % Suppression |
|-------------------|------------------------|---------------|------------------------|---------------|
| untreated control | 410 ± 99 | - | 1234 ± 354 | - |
| Paclitaxel | ^a 289 ± 108 | 30 | 866 ± 348 | 30 |
| Paclitaxel + CI | ^b 182 ± 69 | 56 | ^c 491 ± 151 | 60 |

^a data are from 5 independent evaluations (mean ± standard deviation) in which there were 10 mice/group in each evaluation. Treatment groups received paclitaxel (30 mg/kg) on day 0 and either vehicle or CI (100 μ g/kg) on day 1 and day 8.

25 ^b P≤0.05 versus the untreated group or the paclitaxel only group (Student's t test).

^c P≤0.05 versus the untreated control.

Several evaluations were performed in which tumor bearing mice received only [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino] ethoxy] carbonyl]-L-lysyl]-alanine (100 μ g/kg) on days 1 and 8 after staging (data not

30

shown). In none of these evaluations did [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine by itself inhibit tumor cell growth in nude mice. [R-(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine does not 5 directly inhibit tumor cell growth *in vitro* nor does it potentiate the growth inhibitory effect of paclitaxel in cell culture.

The effects of a bioresponse modifier and a chemotherapeutic agent were also evaluated in a clinical study. [R-(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine was used as a 10 representative bioresponse modifier, and paclitaxel and carboplatin were used as representative chemotherapeutic agents. In this study, cancer patients with late stage disease were given a dose of [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine (cycle 0) 15 approximately 7 days before the first round of chemotherapy (carboplatin and paclitaxel). Patients received a second round of chemotherapy approximately 21 days later and on days 1 and 8 after this 2nd chemotherapy treatment patients received [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine at the doses indicated in table 20 below. Sixty-nine percent of patients showed some clinical benefit either in the form of complete or partial reduction in tumor mass or stabilization of disease. Of the 16 patients treated, 6 had a presumed diagnosis of NSCLC. In this group, there were 3 complete responses, 1 partial response, one stabilization of disease and only 1 patient with progressive disease. Inasmuch as the expected complete response rate with the 25 standard chemotherapy regimen (paclitaxel and carboplatin) is approximately 5%, the finding that 3 of 6 treated patients showed a complete response was completely unexpected. In this treatment regimen, the dose of paclitaxel was 175-200 mg/m² and the dose of carboplatin was the dose at which the area under the curve (AUC) equals 6 mg/ml x min. The results from the clinical trial are summarized in the table 30 below. In the Table below, [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine is referred to as CI.

TABLE 2. Treatment of Advanced Cancer Patients with a Combination of Paclitaxel, Carboplatin and CI.

| # Patients treated | Dose (µg/kg) ^a | "Tumor Response | | | |
|--------------------|---------------------------|-----------------|---------|--------|-------------|
| | | Complete | Partial | Stable | Progressive |
| 3 | 0.1 | 2 | 1 | | |
| 6 | 0.2 | | 1 | 2 | 3 |
| 4 | 0.266 | 1 | 1 | 1 | 1 |
| 3 | 0.4 | 1 | | 1 | 1 |
| Total | 16 | | 4 | 3 | 5 |

^a Complete - no evidence of disease
5 Partial - ≥ 50% decrease in tumor mass
Stable - no further progression of disease
Progressive - disease progressed

^aDose of CI.

10 The results of the in vivo standard pharmacological test procedure and clinical trial using representative bioresponse modifiers and chemotherapeutic agents demonstrate that the combination of a bioresponse modifier with a chemotherapeutic agent is useful in potentiating standard chemotherapeutic regimens and is useful in treating solid tumors. In particular, the combination of this invention is useful in
15 treating non-small cell lung carcinoma, glioma, cancers of the ovary, breast, prostate, head and neck, kidney, pancreas, liver, and colon, and soft tissue sarcoma.

As used in this invention, the combination regimen can be given simultaneously or can be given in a staggered regimen, with the bioresponse modifier being given at a different time during the course of chemotherapy. Therefore, the
20 term combination does not necessarily mean administered at the same time or as a unitary dose. For example, the regimen in the clinical study typifies a therapeutically useful regimen, in which patients received a bioresponse modifier before receiving the first course of chemotherapy. As typical for chemotherapeutic regimens, the course of chemotherapy is repeated several weeks later, and in this case, the
25 bioresponse modifier was administered one or more days after the administration of the second course of chemotherapy. This course of staggered administration can be continued throughout the treatment period.

The components of the combination can be formulated into a unitary dosage form, for simultaneous administration, however, it is anticipated that the components of the combinations will be formulated for separate administration.

Formulations for specific chemotherapeutic agents are well known in the art

5 (and most used will typically be commercially available or already formulated for use in clinical trials), with such agents typically administered intravenously or orally; however, as each agent and patient varies, the chemotherapeutic agents may also be administered by parenteral injection, rectally, vaginally, transdermally, subcutaneously, topically, intranasally, or by direct infusion to the site of the lesion.

10 The bioresponse modifiers of this invention may also be administered orally, intravenously, parenterally, rectally, vaginally, transdermally, subcutaneously, topically, intranasally, or by direct infusion to the site of the lesion. The bioresponse modifiers can be formulated according to standard literature methodology. For example, formulations for the compounds of Formula I and [R-(R*,R*)]-N-[(R)-6-15 carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine are provided in U.S. Patent 5,312,831.

Bioresponse modifiers and chemotherapeutic agents which are not commercially available or available in clinical trials (or in which it is undesirable to use such existing formulations) may be formulated neat or may be combined with one

20 or more pharmaceutically acceptable carriers for administration. For example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to

25 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

30 Formulation for tablet or capsule administration may include solid carriers including starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic

surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

5 These components of the combination may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared

10 10 in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparation contain a preservative to prevent the growth of microorganisms.

15 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol

20 20 (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

It is anticipated that the dosage of chemotherapeutic agents and bioresponsive modifiers will be adjusted during the course of treatment, according to patient response to treatment and toxicity inherent in standard chemotherapeutic regimens.

25 25 For example, the dosage of chemotherapeutic agents is typically lowered upon observation of myelosuppression or impaired hepatic function. As a starting dosage, it is anticipated that the initial dosages of chemotherapeutic agents will be the dosages which would be used absent combination with a bioresponse modifier. For example, for a regimen consisting of paclitaxel, carboplatin and [R-(R*,R*)]-N-[(R)-6-

30 30 carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoethyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine, it is anticipated that the dosage of paclitaxel would be 135-225 mg/m², with 175-200 mg/m² being preferred, and the dose of carboplatin would be the dose at

which the area under the curve (AUC) equals 5-7 mg/ml x min, with 6 mg/ml x min being preferred. Projected dosages of the bioresponse modifiers will vary according to their potency in inducing the immune system; for cytokine inducers, their potency in inducing the production of cytokines. For [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[(2-5) carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine it is anticipated that the initial dosage will range from 0.005 - 2 μ g/kg, with 0.01 - 1 μ g/kg being preferred.

CLAIMS

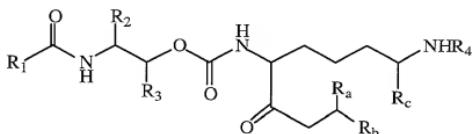
1. A method of treating solid tumor in a mammal which comprises administering to said mammal an effective amount of a combination of a bioresponse modifier and a 5 chemotherapeutic agent.

2. The method according to claim 1, wherein the bioresponse modifier is a cytokine inducer.

10 3. The method according to claim 2, wherein the chemotherapeutic agent is a microtubular agent or a macrophage activating agent.

4. The method according to claim 3, wherein the cytokine inducer is a compound of formula I, having the structure

15



wherein

R₁ is selected from the group consisting of hydrogen, a substituted or unsubstituted 20 (C₁-C₂₀) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or 25 unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

R_a and R_b are independently selected from hydrogen, substituted or unsubstituted (C₁-C₆) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R_b, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;

10 R₂, R₃ and R₄ are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxamide; X is oxygen or nitrogen;

15 R₄ is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyaryalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxy carbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfinyl, aralkylsulfinyl, 20 lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1-4 hetero atoms selected from nitrogen, sulfur and oxygen;

25 5. The method according to claim 4, in which the compound of formula I is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

30 6. The method according to claim 5 wherein the microtubular agent or macrphage activating agent is selected from the group consisting of paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, adriamycin, doxorubicin, cisplatin, carboplatin, mitomycin C, and bleomycin.

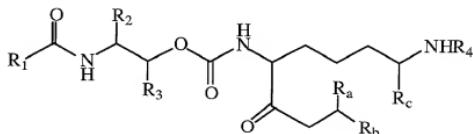
7. The method according to claim 6, wherein the microtubular agent or macrophage activating agents are paclitaxel and carboplatin.

5 8. A method of potentiating the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a chemotherapeutic regimen.

9. The method according to claim 8, wherein the bioresponse modifier is a
10 cytokine inducer.

10. The method according to claim 9, wherein the chemotherapeutic agent is a microtubular agent or a macrophage activating agent.

15 11. The method according to claim 10, wherein the cytokine inducer is a compound of formula I, having the structure



I

20 wherein

R₁ is selected from the group consisting of hydrogen, a substituted or unsubstituted (C₁-C₂₀) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted

monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

R₂ and R₃ are independently selected from hydrogen, substituted or unsubstituted (C₁-C₆) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted

5 cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R₃, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH-X-- moiety;

10 R₂, R₃ and R₄ are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxamide;

X is oxygen or nitrogen;

15 R₄ is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyarylalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, 20 loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfinyl, aralkylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1- 4 hetero atoms selected from nitrogen, sulfur and oxygen;

25 or a pharmaceutically acceptable salt thereof.

12. The method according to claim 11, in which the compound of formula I is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

30

13. The method according to claim 12 wherein the microtubular agent or macrphage activating agent is selected from the group consisting of paclitaxel,

docetaxel, vincristine, vinblastine, vinorelbine, adriamycin, doxorubicin, cisplatin, carboplatin, mitomycin C, and bleomycin.

14. The method according to claim 13, wherein the microtubular agent or
5 macrophage activating agents are paclitaxel and carboplatin.

ABSTRACT

This invention provides a method of treating solid tumors which comprises administering an effective amount of a combination of (1) a bioresponse modifier and (2) a chemotherapeutic agent. This invention also provides a method of potentiating 5 the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a chemotherapeutic regimen.

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Method of Potentiating Chemotherapy and Treating Solid Tumors the specification of which

(check one) X is attached hereto.

_____ was filed on _____ as
Application Serial No. _____
and was amended on _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed
Yes No

(Number) _____ (Country) _____ (Day/Month/Year Filed) _____

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

Not Yet Known September 15, 1999 which was converted from U.S. Patent Application
(Provisional Appln. No.) (Filing Date) No. 09/396,051, filed September 15, 1999, pursuant to a petition filed under 37 C.F.R. 1.53(c)(2)(i).

(Provisional Appl. No.) (Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.) (Filing Date) (Status - Patented, pending, abandoned)

(Application Serial No.) (Filing Date) (Status - Patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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